REMARKS

Claims 1 to 15, and 17 to 22 are in the application. Claim 16 has been cancelled. Applicant reserves the right to file continuation applications on cancelled or deleted subject matter. Support for Claims 17 and 18 lie in the originally filed claims and the examples. No new matter is believed added. The amendment to the specification for a claim to priority of the parent applications was requested in Applicants Transmittal Letter of 13 February 2002, thereby completing the requirements of 35 USC §120. However, as the Examiner has indicated in the present office action that the references to such information are missing Applicants again amend the specification.

The Examiner has also requested a new Abstract. While it is suggested that the Abstract include a Figure, there are no drawings present in this application. Applicants have amended the Abstract to include Claim 1. No new matter is believed added.

Rejections under 35 USC §102(b)

The Examiner has rejected claim 16 under 4 different references as being anticipated under 35 USC §102. The four references are Ortega et al., US Patent 4,737,585; Callander, US Patent 3,926,958; Corsi et al, EP 0 596 262 and Cabre et al., WO 97/15579. Applicants respectfully traverse these rejections.

Claim 16 is directed to a product by process claim. Applicants fully recognize that crystalline sodium amoxycillin is known in the art as evidenced by the very references cited. However, the process of making crystalline sodium amoxycillin by the synthetic steps of claim 1 is believed novel and therefore the product obtained by those steps should also be allowable. However, in order to advance prosecution the merits, Applicants have cancelled claim 16 rendering this rejection moot.

Rejection under 35 USC §103(a)

Claims 1 to 9 are rejected as being unpatentable over Ortega et al., US Patent 4,737,585 ('585 patent). Applicants respectfully traverse this rejection.

A major differences between the claimed process and the '585 patent involves the steps up to and including the dissolution of amoxicillin. The present claims require 3 steps and each step has its own purpose. By suspending the amoxicillin in methyl acetate, there is a decrease in the amoxicillins' particle size in preparation for the next step. Triethylamine (TEA) is added to the fine suspension of the first step. The mixture thickens as the amoxicillin-TEA adduct is formed. Methanol is then added and the amoxicillin dissolves instantly and completely in this solvent.

In contrast, the '585 patent essentially uses a brute force approach to effect dissolution. Large amounts of alcohol's, in particular methanol were used for the

dissolution. In addition to this not being needed by the present invention, the '585 process also reduces the product yield by increasing solubility of amoxicillin in the mother liquor.

The primary differences between these two processes are summarized in the table below:

Step	US Patent 4,737,585	Claimed Process	Difference
Suspension	Suspension is performed in a mixture of aprotic organic solvent and alcohol.	Amox trihydrate is suspended freely in methyl acetate. This allows all agglomerates to break up prior to reaction with triethylamine.	'585 patent doesn't use methyl acetate. '585 patent uses an alcohol co-solvent in the suspension step.
TEA salt formation	TEA is added with alcohol present. Methanol dehydrates the surface of the amoxicillin trihydrate agglomerates. This competing reaction increases the time needed for complete dissolution.	TEA salt is formed without alcohol present. The amoxicillin TEA adduct is finely suspended in the methyl acetate.	As the claimed process does not have methanol present yet, it avoids the formation of a "crusty" dehydrated amoxicillin trihydrate.
Dissolution	Combined with TEA salt formation	Methanol is added and the amoxicillin is dissolved instantly.	Since the dissolution is faster in the claimed process there is less time for degradation to occur. The process as described herein also uses less methanol which provides for a higher yield.
Crystallization	Sodium diethoxyacetate is the salifying agent	Sodium 2-ethyl hexanoate is the salifying agent	

Newly added claims 17 to 22 are believed to more particularly point out and distinctly claim the process point differentiations between the '585 patent and the disclosed invention.

The Examiner comments that the "process is obvious over that taught in the reference because changing the order of steps in a known multi-step process does not make the process unobvious when no unexpected results occur" (page 5 first full paragraph, Office Action 06/02/2003). The present invention, as can be seen from the table above produces a greater yield of final product than that of the '585 patent. Example 1 of the present invention, page 6 discloses a product yield of 89.7 to 93.6%. This is in contrast to a yield of about 74%, see Example 8 of the '585 patent..

This result is not taught nor suggested by the '585 reference. The '585 patent does not suggest the use of methyl acetate as a solvent for the first suspension step; nor does the '585 patent teach formation of the TEA salt without use of alcohol being present.

Consequently, the '585 patent does not suggest to the skilled artisan the series of steps as claimed herein.

In view of these remarks, reconsideration and withdrawal of the rejection to Claim 1 to 9 is respectfully requested.

Rejection under 35 USC §103(a)

Claims 1 to 14 are rejected under 35 USC §103(a) as being obvious over Callander US Patent 3,926,958 ('958). Applicants respectfully traverse this rejection.

Similar to the analysis above, the major differences between the claimed process and the '958 patent involve the steps up to and including the dissolution. The claimed process has 3 steps and each step has a purpose. By suspending the amoxicillin in methyl acetate, there has been found to be a decrease in its' particle size in preparation for the next step. Triethylamine is then added to the fine suspension created in the first step. The mixture thickens as the amoxicillin-TEA adduct is formed. Methanol is added to this mixture and the amoxicillin dissolves instantly and completely.

US Patent 3,926,958 complexes the amoxicillin trihydrate with a mixture of an amide, such as dimethylacetamide or dimethylformamide, and an alcohol. The mixture is then dissolved with a mixture of diethylamine and an alcohol.

As with the '585 patent the '958 patent also takes a brute force approach to effect dissolution. Large amounts of alcohol's were used for the dissolution. In addition to this not being needed, this also reduces product yield by increasing solubility in the mother liquor.

Step	US Patent 3,926,958	Claimed Process	Difference
Suspension	Suspension is performed in a mixture of an amide (DMA or DMF) and alcohol. The amoxicillin complexes with the amide.	Amox trihydrate is suspended freely in methyl acetate. This allows all agglomerates to break up prior to reaction with triethylamine.	'958 doesn't use methyl acetate. '958 uses Dimethyl-acetamide and dimethylformamide. '958 uses an alcohol - amide mixture in the suspension step.
Amine salt formation	Diethylamine is added with alcohol present. This competing reaction increases the time needed for complete dissolution.	TEA salt (complex) is formed without alcohol present. The amoxicillin TEA adduct is finely suspended in methyl acetate.	
Dissolution	Combined with DEA salt formation	Methanol is added and the amoxicillin is dissolved instantly	Since the claimed process results in a faster dissolution, there is less time for degradation to occur. The process also

			requires less alcohol, which provides for a higher yield.

The present invention, as can be seen from the table produces a greater yield of final product than the '958 patent. Example 1 of the present invention, page 6 discloses a product yield of 89.7 to 93.6%. This is in contrast to yields of about 75%, see Examples 1 to 4. This result is not taught nor suggested by the '958 reference. The '958 patent does not suggest the use of methyl acetate as a solvent for the first suspension step; nor does the '958 patent teach formation of the TEA salt without use of alcohol being present. Consequently, the '958 patent does not suggest to the skilled artisan the series of steps as claimed herein. Similarly, the newly added claims also point out the differences between the process steps of the '958 patent and the disclosed invention.

In view of these remarks, reconsideration and withdrawal of the rejection to Claim 1 to 14 is respectfully requested.

Rejection under 35 USC §103(a)

Claims 1 to 9, 11, 12 and 15 are rejected under 35 USC §103(a) as being obvious over Corsi, EP 30 596,262 A1 ('262), and Claims 1 to 15 are rejected over Cabre (WO 97/15579 A1). Applicants respectfully traverse these rejections.

Similar to the comments above, the reference teaches use of an alcohol, methanol or ethanol specifically for preparation of the salt form of amoxicillin. This clearly is a different step than the presently claimed invention, and in particular Claims 17 to 22. As noted above, it is the overall combination of 3 steps which produces the improved yield and product characteristics. Corsi provides, for instance, yields of 75% to 80%, see Examples 1 & 2.

Consequently, in view of these remarks, reconsideration and withdrawal of the rejection to the claims is respectfully requested.

CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

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